

FEATURED CASE REPORT

Long QT syndrome and life threatening arrhythmia in a newborn: molecular diagnosis and treatment response

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Intrauterine and neonatal manifestations of congenital long QT syndrome are associated with a high cardiac risk, particularly when atrioventricular block and excessive QT prolongation ($> 600 \text{ ms}^{1/2}$) are present. In a female newborn with these features, treatment with propranolol and mexiletine led to complete reduction of arrhythmia that was maintained 1.5 years later. High throughput genetic analysis found a sodium channel gene (LQT3) mutation. Disappearance of the 2:1 atrioventricular block and QTc shortening (from $740 \text{ ms}^{1/2}$ to $480 \text{ ms}^{1/2}$), however, was achieved when mexiletine was added to propranolol. This effect was considered to be possibly genotype related. Early onset forms of long QT syndrome may benefit from advanced genotyping.

Congenital long QT syndrome (LQTS; prevalence about 1 in 5000) is a primarily familial disease with an autosomal dominant mode of disease transmission. In 12% of patients with LQTS, sudden death may be the first manifestation of the disease and, importantly, in 4% it may happen in the first year of life.¹ The presence of a very long QT interval ($> 600 \text{ ms}$), T wave alternans, 2:1 atrioventricular (AV) block, and inner ear deafness are proposed to indicate infants with a high cardiac risk.²⁻³ In neonates, LQTS is a rare finding but fetal arrhythmia may already occur during pregnancy.⁴⁻⁵ These observations led to the hypothesis that LQTS may be linked to a subset of sudden infant death syndrome (SIDS).⁶ Recently, several reports finally showed the presence of LQT gene mutations in cases of SIDS or near miss SIDS⁷⁻⁸ and thereby provided the molecular link between severe arrhythmia syndromes and SIDS. LQTS is a genetically heterogeneous ion channel disorder⁹ in which mutations either in cardiac potassium channel genes or in the cardiac sodium channel gene *SCN5A* (LQT3) cause the disease. β Receptor blocking agents are the treatment of choice for most LQTS patients, potentially even in asymptomatic children.² Sodium channel blockers have specifically been proposed for treatment of the LQT3 subform, since in these mutations addition of sodium channel blockers, mostly but not exclusively in vitro, resulted in a gain of channel function (with a sustained, non-inactivating sodium current that can be suppressed by sodium channel blockade). In the present study, we report on a newborn with congenital LQTS who was severely threatened by perinatal arrhythmias and who was effectively treated after an LQT3 mutation was considered and finally identified.

MATERIAL AND METHODS

Phenotyping

The diagnosis of LQT syndrome was based on common criteria.¹⁰ Repolarisation features (ST segment and T wave

morphology) in the surface ECG first led to consideration of the LQT3 subtype. Both parents gave written informed consent for genetic analyses. The study was conducted in accordance with the Declaration of Helsinki and recommendations given by the university's local ethics committee.

Genotyping

Standard methods for genetic analysis were used as previously described.¹¹ The BigDye RR Terminator AmpliTaq kit, together with the ABI Prism 3700 Genetic Analyzer (both Perkin-Elmer Applied Biosystems, Weiterstadt, Germany), was used for sequence determination. Nucleic acid deviations were compared with the reference sequence for *SCN5A* (Genome Database, GI:4506808; GenBank, NM_000335) and confirmed by sequencing of both strands. Identified novel sequence alterations were investigated for their presence in a control group (more than 200 chromosomes¹¹). When a de novo mutation (not present in either parent) was present in a child, paternity was determined with the AmpFISTR Profiler Amplification Kit (Perkin-Elmer Applied Biosystems).

RESULTS

Clinical course of a newborn with congenital LQTS

The female newborn, the first child of non-consanguineous healthy parents (mother's QTc $430 \text{ ms}^{1/2}$, father's QTc $410 \text{ ms}^{1/2}$) (fig 1), was born at week 35 of gestation by caesarean section because of intrauterine episodes of fetal bradycardia and tachycardia. After birth, the baby's Apgar scores were 7 (minute 5) and 9 (minute 10). The neonate had a hydrops fetalis leading to overweight for age (3440 g). Also, a slow heart rate (50 beats/min) and cardiopulmonary failure were noted, requiring assisted ventilation for six days. ECG recordings had an extremely long QT interval (QTc $740 \text{ ms}^{1/2}$) in the setting of a second to third degree AV block (ventricular rate about 80 beats/min; not shown). Recurrent episodes of non-sustained, polymorphic ventricular tachycardia (torsade de pointes type; 300 beats/min) occurred. At day 1, the neonate was admitted to the paediatric department; generalised oedema and pleural effusions were present and transthoracic echocardiography showed reduced contractility (fractional shortening 18%) of a normal sized left ventricle without signs of structural heart disease. Short runs of torsade de pointes tachycardia reoccurred but electrical defibrillation was not required. Intravenous propranolol was initiated (maximum dosage 4 mg/kg/day) but was only partially effective in suppressing ventricular tachycardia. AV block, however, persisted. Because of the ECG phenotype (long QT interval together with an isoelectric ST segment and

Abbreviations: AV, atrioventricular; LQT3, sodium channel gene; LQTS, long QT syndrome; SIDS, sudden infant death syndrome

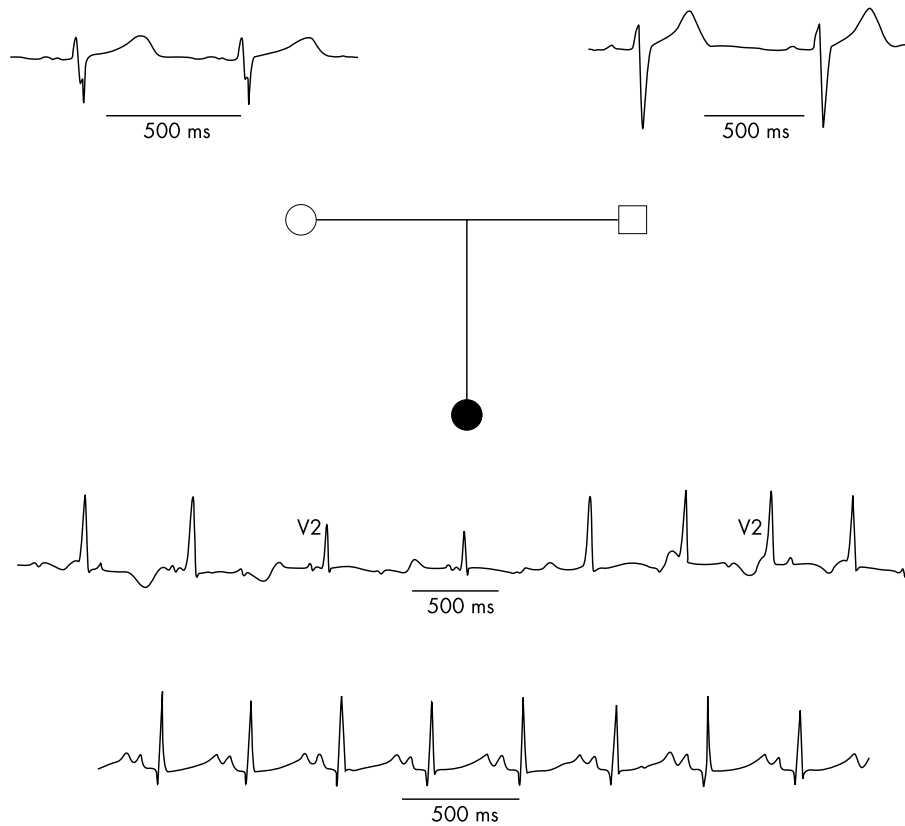


Figure 1 Pedigree and surface ECGs of a family with a de novo long QT syndrome. Both parents had sinus rhythm and normal time intervals (mother's QTc interval (I-I) 430 ms^{1/2}, father's (I-2) 410 ms^{1/2}, lead V2). In contrast, the child (II-1) had a 2:1 atrioventricular block and remarkable QTc prolongation (QTc 700 ms^{1/2}, lead V2) on the first day of life (upper panel). During treatment with mexiletine and propranolol (day 28) regular atrioventricular conduction was achieved together with a shortening of the QTc interval (510 ms^{1/2}, lead II; lower panel). The patient was free of episodes of ventricular tachycardia. Bold symbol: affected; circle: female sex; square: male sex.

a normal T wave), the LQT3 subtype was suspected and intravenous mexiletine was started (cumulative dosage at day 1 was 12 mg/kg/day). To prevent bradycardia related triggering of ventricular arrhythmias, a cardiac pacemaker (VVI mode, 130–110 beats/min) with epimyocardial leads was implanted. Under the cumulated high dosage of mexiletine AV block disappeared and sinus rhythm was established. After day 2, no ventricular tachycardia occurred and QTc was greatly shortened (480 ms^{1/2}) (fig 1). Cardiac function improved to normal and the patient was discharged on day 28 (mexiletine 8 mg/kg/day; propranolol 4 mg/kg/day). During a follow up period of 1.5 years, the patient remained asymptomatic.

Molecular diagnosis of a LQT3 syndrome

Because of the ECG phenotype (fig 1), all coding regions of the LQT3 gene *SCN5A* were first sequenced directly. In exon 23, a heterozygous C to T transversion at nucleotide position 3995 was detected (strand + opposite strand) in the index patient (fig 2). No other mutations were detected in *SCN5A*. This nucleotide exchange was predicted to cause an amino exchange from proline to leucine at residue 1332 (P1332L; S4-S5 linker of DIII) and is located within a highly conserved protein region (alignment data not shown). In a large control population, the 3995T allele was absent, making a rare polymorphism improbable. Since the mutation (P1332L) was also not identified in both parents (fig 3), we considered it to be a de novo mutation after paternity was determined to be very likely. The mutation was indicated by 10 short tandem repeat markers from different chromosomal loci.

DISCUSSION

In the present case, prenatal episodes of severe arrhythmia were recorded during cardiotocography that required premature birth of a neonate with LQTS. Only a few reports of

early onset LQTS are known. Here, we identified a specific sodium channel mutation (P1332L; fig 2) in the setting of an effective, combined medical treatment during follow up.

Fetal manifestations of LQTS may include sinus bradycardia, AV conduction block, and ventricular tachycardia, recordable by magnetocardiography or cardiotocography.^{3–5} Neonates with a very long QT interval (> 600 ms^{1/2}), a 2:1 AV block, or both (as seen in the present case) (fig 1) are at a particularly high cardiac risk² and require immediate and effective treatment. The QTc interval of the present neonate (740 ms^{1/2}) is one of the longest reported so far; the observed 2:1 AV block was most likely functional ("pseudo" AV block) because P waves occurred before the end of the T wave (fig 1) and resolved at slower sinus rates (fig 1). Similar cases of LQTS have been reported.^{4 12–16} Electrophysiological studies suggested an infra-Hisian location of the block.^{15 16} Histomorphological changes of the conduction system are also known in congenital LQTS.^{17 18}

During high dose treatment with propranolol sinus rhythm was not established in the proband, although this treatment has been shown to be effective in newborns with LQTS.¹⁹ We questioned whether these different therapeutic responses may be related to different genetic causes of LQTS.²⁰ We finally found a heterozygous amino exchange (P1332L) in the *SCN5A* gene of the proband that suggested that the disease was causative, since, firstly, the mutation was not present in both healthy parents (de novo mutation); secondly, the possibility of a rare polymorphism was determined to be unlikely by investigations of controls; and thirdly, the amino acid residue was evolutionarily conserved (and thereby probably functionally important). Recently, Wedekind *et al*⁸ identified in an adjacent residue a missense mutation (A1330P) in a patient with neonatally manifesting LQTS who died of a documented cardiac arrest despite high dose propranolol. The specific mutation, in contrast to other LQT3

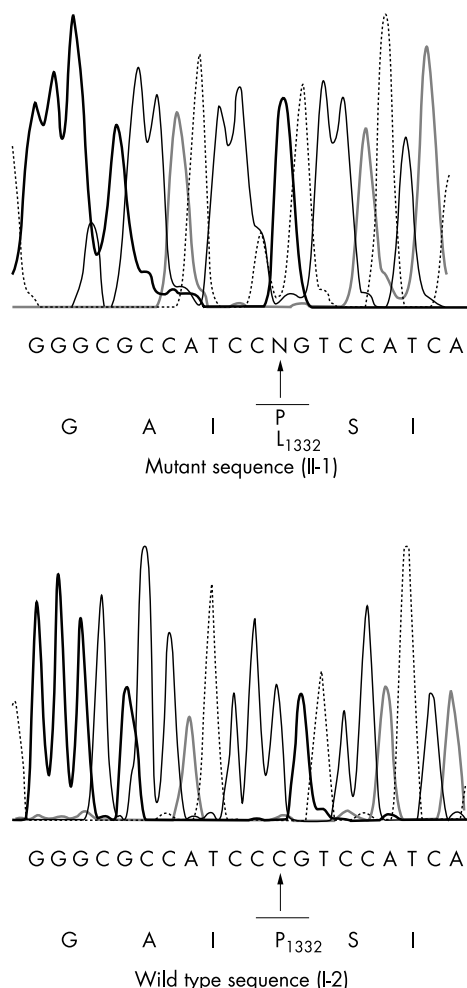


Figure 2 Mutation detection in the *SCN5A* gene: sequence analysis of exon 23. A heterozygous C to T transversion at nucleotide position 3995 was detected in the index patient (upper part of the panel) and was confirmed by sequencing of the opposite strand. This nucleotide exchange was predicted to cause an amino exchange from proline to leucine at residue 1332 (P1332L). The mutation was not identified in the child's parents. The wild type conformation of the corresponding sequence of exon 23 as detected in the father (I-2) is shown in the lower part of the panel.

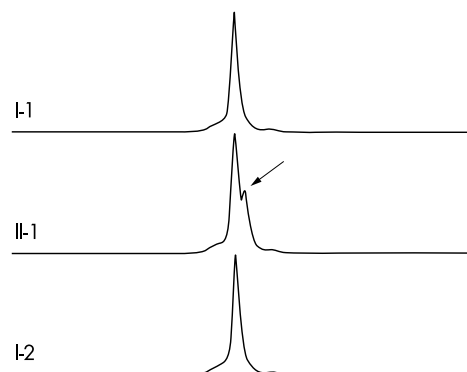


Figure 3 Mutation detection in the *SCN5A* gene: single strand conformational polymorphism analysis of exon 23. The configuration was normal (wild type) in the child's parents (I-1 and I-2). In contrast, a migration shift (arrow) was observed in the child that corresponded to the heterozygous P1332L mutation that arose de novo.

mutations, augmented the sodium current in vitro by increasing current amplitude (due to acceleration of channel recovery from inactivation and slowing the channel's inactivation). The P1332L mutation may potentially exhibit similar electrophysiological characteristics, but this has not been shown. In contrast to the case reported by Wedekind *et al.*⁸ the present neonate was additionally, and potentially successfully, treated with mexiletine, most likely resolving the functional AV block (fig 1) and thereby shortening the QTc interval (from 740 ms^{1/2} to 480 ms^{1/2}) (fig 1). Interestingly, pacemaker interrogation further showed that cardiac pacing of the neonate was not needed under this combined treatment.

So far, only limited data are available about neonatal manifestation and treatment of LQTS in relation to specific genotypes. Very recently, Yao and colleagues²¹ reported on a similar case of neonatal LQTS in which a combination of mexiletine and propranolol was effective in suppressing cardiac arrhythmias over a period of two years. Unfortunately, the genotype of this patient was not reported. Conclusions, however, still have to be drawn carefully. We therefore propose that infants with fetal arrhythmias or a postnatal QTc interval > 500 ms^{1/2} during repeated ECG recordings²² undergo genetic testing to identify early those with the LQT3 variant, who specifically may benefit from additional sodium blocker, as in the present case. The patient's investigation should include Holter monitoring of the proband and investigation of the family. Even when the parents are unaffected or the family history is unremarkable, immediate genetic testing may be still of value to support the clinical diagnosis and to confirm a de novo onset of the disease that, on the other hand, has implications for the probability of identifying other mutation carriers in the family.

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IMAGES IN CARDIOLOGY

Calcium channel blocker induced gum hypertrophy: no class distinction

A 49 year Afro-Caribbean man, with a 10 year history of resistant hypertension, was referred for further management on the following medications: amlodipine 20 mg, atenolol 200 mg, and enalapril 60 mg daily. Other treatments comprised: two-weekly moderate injections, procyclidine, and nocturnal temazepam 10 mg for stable schizophrenia. He had acquired a degree of renal impairment (creatinine clearance of 64 ml/min) as a result of his hypertension, but was not actively requiring dialysis. Pronounced gum hypertrophy with bleeding was a key initial clinical finding (below left). Withdrawal of the dihydropyridine calcium channel blocker resulted in slow regression of the gum hypertrophy. The blood pressure continued to be poorly controlled despite the use of six different antihypertensive drug classes (β blocker, α blocker, angiotensin II receptor blocker, potassium sparing diuretic as well as a loop diuretic, and a centrally acting agent). A non-dihydropyridine

calcium channel blocker (diltiazem XL 240 mg daily) was therefore prescribed to try to improve the blood pressure. Unfortunately the gum features worsened again over a period of three months. They resolved several months after calcium channel blocker withdrawal (below right).

Gum hypertrophy is a well recognised side effect of dihydropyridine calcium channel blockers, with few reports following non-dihydropyridine calcium channel blockers. This case illustrates that it may occur with both major classes of calcium channel blockers and resolve following their cessation.

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